

## VITAMIN D: AWONDER PILL

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### ABSTRACT

Vitamin D has received global attention not only because of its importance in bone health but also for its reducing risk of many diseases like heart problems, autoimmune disease, and many cancers. It's remarkable effect on diabetes (types 1 and 2), high blood pressure, multiple sclerosis and many infectious diseases has become the talk of town worldwide. Scientists are currently working on its effects in serious and end-stage diseases.

In today world, Vit-D deficiency is pandemic, due to the fact that we humans are dependent on the sun for Vit-D requirement, but high blazing heat forces us to avoid the sun, by applying sun block or by wearing sun protection for fear of skin cancer. Every 4th individual out of 10 people don't have enough Vit-D either due to lack of exposure of sun or lack in eating enough food with vitamin D in it or might have some health-related issue which stops its absorption. Few foods contain vitamin D naturally while some have fortified with it. Every food has different content of Multivitamins, same goes with Vit-D. Adequate serum calcium and phosphorus is required from proper mineralization of strong bones, without Vit-D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed [8-10] making bones fragile or porous and easy to break.

Keeping in mind the great role of Vitamin D, following a general literature review on its deficiencies, source of intake, and its involvement with other health problems. An overview of major meta-analyses of vitamin D is given. This systematic approach covers metaanalyses listed in Pubmed during the past 2 decades.

**Keywords:** Vitamin D3 (cholecalciferol), Vitamin D2 (ergocalciferol), Vitamin D (Calciferol),

### INTRODUCTION:

Vitamin D is a pro hormone from fat soluble group, vitamin D were identified in start of 20th century during the anti rachitic effects of cod liver oil. The name "D" was suggested after discovery of A, B

and C which were discovered earlier [1]. No doubt we all are familiar with the benefits of Vitamin D, but VitD was long neglected beside Vit C and E, which are considered hearts of many supplement lovers. But now these kings of supplements share their throne of deserved attention with Vit D. In fact, there are real benefits to increasing your Vit D.

The Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol) are two major biological precursors of Vitamin D (Calciferol) [2,3]. Vitamin D is naturally found in some food, sometimes added to others and available as dietary supplement. Vitamin D is endogenously formed in the body when 7-dehydrocholesterol in the skin is exposed to sunlight (UV light, UVB, 290-320nm) it triggers the synthesis of Pre vitamin D [5]. Vitamin D2 is a plant-driven compound; it is exogenously produced from ergosterol irradiation. It gets inside our body through diet. Both vit D precursors driven by sunlight exposure and diet are converted into 25-hydroxyvitamin D [25(OH)D] (calcidiol) inside the liver. This pre vitamin D undergoes a liver-dependent process to convert into Vit D when they enter the liver [4]. The 25(OH)D is the major circulating form of Vit D, and used as a determinant of Vitamin D status. Additional hydroxylation in the kidneys is done to form the biologically active metabolite 1,25-dihydroxyvitamin D [1,25(OH)2D] (calcitriol) [5]. This compound has a long circulating half-life of 15 days in the blood stream [6,1]

Excess exposure of UVB rays changes pre vitamin D into tachysterol and lumisterol which are biologically inactive metabolites of Vit D.

Vitamin D3 and D2 are the most important group of Vit D present in humans and animals. VitD is responsible for many biological effects; it helps in the absorption of many micronutrients, like Calcium, magnesium, phosphate and many others. The absorption of calcium is dependent on Vit-D, adequate serum calcium maintains normal bone mineralization and prevents hypocalcemic tetany (involuntary contraction of muscles, leading to cramps and spasms).

VitD has many other functions, like cell growth modulation, neuromuscular and immune functions. It has a great role in the reduction of inflammation and glucose metabolism [1,3]. Vit D also modulates many proteins which are responsible for the regulation of proliferation, differentiation and apoptosis. Vit D receptors are present on many tissues of the body, which helps in the conversion of 25(OH)D to 1,25(OH)2D.

### **Source of Vit D**

Major source of Vit D is sunlight exposure. But humans obtain Vit D from dietary intake as well, although very few natural foods have vitamin D. Oily fish such as mackerel, salmon and sardines are rich sources of Vit D3, and fish liver oil is another rich supplement. Egg yolks are reported to have Vit D, though their amounts are quite variable depending upon type and size of eggs. Moreover, the cholesterol content of egg yolk makes it a poor source of Vit D. Whereas some foods are fortified with Vit D, such as milk, some citrus fruit juices, bread and cereals [6,8].

### **Dose of Vit-D**

The Institute of Medicine made its dose recommendations based on a population-based model; the Endocrine Society's Practice Guidelines on Vitamin D was given for the prevention and treatment of

vitamin D deficiency [23,25]. The Guidelines defined vitamin D deficiency as a 25- hydroxyvitamin D , 20 ng/mL, insufficiency as 21–29 ng/mL and sufficiency as 30–100 ng/mL. To prevent vitamin D deficiency The Guidelines recommended vitamin D intake should be: children, 1 y 400–1,000 IU/d, children 1–18 y 600–1,000 IU/d and adults 1,500–2,000 IU/d. coming towards natural source of Vit-D, a table spoon of Cod liver has a 1360 IU of Vit-D. if that doesn't sound succulent to you, try foods like swordfish, salmon, tuna, and sardines, they are richest with Vit-D among all others. Dairy products like yogurt, milk and cheese, and orange juices are good choices too. So are beef liver, egg yolks and fortifies cereal.

Serum 25(OH) D concentrations is assessed for measurement of Vit D levels, the most common assays used by laboratories that conduct the analyses are antibodies or chromatography) [5,6]. Variables are expected in results, depending on which assay is used in the laboratory.

In contrast to 25(OH)D, circulating 1,25(OH)<sub>2</sub>D is generally not a good indicator of vitamin D status because it has a short half-life measured in hours, and serum levels are tightly regulated by parathyroid hormone, calcium, and phosphate [1]. Levels of 1,25(OH)<sub>2</sub>D do not typically decrease until vitamin D deficiency is severe [2].

The international Standardization Program of Vitamin D has developed procedures for standard laboratory measurement of 25(OH)D to improve clinical and public health practice [5,7-10].

## **VITAMIN- D AND HEALTH**

### **Vit-D and Depression**

Although no proven studies are present, but the some authentic studies show link between Vitamin D and Depression. Experts are working, if Raising Vitamin D levels can boost moods, and can prevent depression, or prevent its worsening

### **Vit-D Fights the Flu**

Researchers are still figuring out how exactly Vit D can treat or prevent us from getting flu or common cold virus. One study showed taking vitamin D drops in the winter helped lower the number of Japanese school going children who got the flu. From this it is very much clear that Vit-D play potential role in healthy immune system built up. Our body cannot fight with germs and virus with Vit-D

### **Vit-D Helps Heart**

There's no proven study for Vit-D to lower the risk of heart attack or stroke in humans. But there are some meta analysis on animals which shows positive results. So we hope Vit-D might head off heart failure in human as well. Researchers are looking into it.

### **Vit-D and Cancer Connection**

Vit-D can fight cancers like colon, breast and prostate. The results are best with Vit-D is given in pair with calcium. In one clinical trial, African Americans' risk went down 23% when they took vitamin D supplements [9,11].

### **Vit-D as Bone Builder**

We all are probably familiar with role of Vitamin D in promoting healthy bones, because absorption of calcium in bone is only possible in presence of Vit-D. Lona Sandon, RD, assistant professor of clinical nutrition at the University of Texas Southwestern in Dallas says that if one has deficiency of vitamin D in late years of life, it can leads to bone softening in form of osteoporosis or osteomalacia [15]. Vit-D affects every third women between the ages of 60 and 70 and two third of women between 80 or older. There is no single cause for female to develop bone softening, fall in hormone like estrogen in late age of life can cause this, but Vit D deficiency makes it harder to use the calcium and minerals that can make strong bones. Vit-D can slowdown bone loss. It keeps at bay osteoporosis (porous bone, easily breakable) and lowers your chance of broken bones, bone loss, bone pain.

### **Vit- D and Rickets**

In years to come, city pollution could be thick enough to block most of the sunlight. This cause low vitamin D levels in children, this leads to an epidemic of children's bone soften and misshaping of their growing bones. Exposure to sun and having Vit-D fortified food items helped stop it, but rickets can still develop. It is especially possible in babies of severely low, or Vit-D deficient mothers. Sometimes race favors this deficiency too.

### **Vit-D and Osteomalacia**

Unlike Rickets, which is a common childhood disease, Osteomalacia can develop at any stage of life. We don't only need Vit-D for our bone growth, we still need Vit-D for its repair and maintenance even after its growth is stopped. Low levels can soften your bones, causing them to break and develop problems especially at your hip bones [47].

### **Vit-D and Wound Healing**

Vit D play great role in wound healing, this is particularly true and proven in case of burns. Studies proved that vitamin d supplements helps people recover from burns more effectively than those who are not on Vit D supplements [16,17].

### **Vit-D and Muscle Pain**

People who have low levels of Vit D are more likely to develop bone and muscle problem in late years of life [20]. Weak muscle can increase chancing of falling and breaking a bone. It could be a warning sign, and can be prevented with daily dose of supplement, or change of diet and lifestyle. Vit-D supports your muscles and nerves.

### **Vit-D and Immunity**

MS is autoimmune disease, which attacks central nervous system of body. Its etiology is unknown. Studies shows vitamin D can lower the incidence of MS. If someone already has MS, it can ease symptoms and even slow down the progression of disease. Vitamin D is very crucial for immune system.

## **WHO ARE AT RISK OF VIT-D DEFICIENCY**

### **Breastfed Infants**

Breast feed is considered as white gold. It is first feed of babies and God has blessed this food with all nutrition which baby may need in early years of life. But there is not enough vitamin D in breast milk, to keep babies bone strong. Unless the breast feeding mother does not take Vit D supplement, baby will face vit d deficiency. Breast fed children most often develop Rickets. African American mothers are inclined to have with low Vit D in their blood [22]. Experts say breast feeding children need extra 400 IU of vit D per day [25].

### **People with Bowel Problems**

Vitamin D has 2 forms, which is found in food and dietary supplement. Both forms are chemically different in respect to their side chain structure. Both forms are absorbed in small intestine. This absorption is done by passive diffusion and it involves membrane bound intestinal carrier proteins [26]. The co existing fat in the gut enhance Vit D absorption. But Inflammatory bowel disease (IBD) and other conditions that affect your gut morphology, like celiac disease and cystic fibrosis, may effects its absorption but some vitamin D is absorbed even without dietary fat. Neither aging nor obesity alters vitamin D absorption from the gut, sometimes supplements seems to help in such cases [4, 28]. Body needs fats to get more use of Vit-D

### **People with Gastric Bypass**

Now a day, it's become trend to get gastric bypass done. It is the procedure which people get done in order to get in shape, by cutting / getting rid of part of your GUT. What this do? It will make you feel fuller faster and let you eat fewer calories, but what is drawback of this procedure, with removal of some part of GUT, we also loose that ability of absorb nutrients. Every part of GUT is designed to absorb nutrition from Food which we eat. After gastric bypass it is harder to absorb nutrients like vitamin B12, copper, zinc, calcium, and vitamin D. although we can always get daily vitamins Supplements to keep our levels in normal range. If you want to shed some pounds try taking vitamin D supplements. When vitamin D is taken along calcium, it can keep you from feeling hungry as often, this will help you eat fewer calories [31].

### **People who Are Obese**

If you are obese or your BMI is more than 30 or more, then more likely your vitamin D would be lower than those who are not obese. It is not that your skin makes less vitamin D if you are obese, but the extra fat lying under your skin takes most of the absorbed vit D and very less goes into your main stream of blood, making is level to drop. Therefore diet, and lifestyle change makes a difference.

Other risk factors may include, age 50 or older, having dark skin like black people in the U.S. they have lower levels of Vit-D than their white peers, as darker skin has natural pigment as sun protection, so they need more and longer exposure duration to synthesize Vit-D in their body. Having northern homes and milk allergy / lactose intolerance can also be added in risk factors for Vit-D synthesis along with certain medications such as medicine for seizure.

## **CONCLUSION:**

### **Keep check on Your Vitamin D**

It is good to know the problem, before actually having it in yourself. Deficiency of Vit-D can be harmful. Evidence shows the links of increasing incidence of type 1 diabetes, muscle and bone problem, and more serious issues like cancers of breast, colon, prostate, ovaries, esophagus and lymphatic system. A simple blood test can help you keep a tab on your vit D levels. Now question arise, when can one get his/ her Vit D level checked? Consider a test when you face signs of Vit D deficiency, like bone pain, muscle pain, or you have low exposure of sun, or you are house bound. Always remember, if your levels are low, never overdo supplements to make up the deficiency. Too much can be harmful too.

If one wants to keep their blood pressures under control, or keep diabetes under check, or simply lowering the risk of heart problem, failure or strokes, or want to stay away from bone problem like rheumatoid arthritis, or multiple sclerosis, then vitamin D is just what you need. Make a habit of putting vitamin D at the frontline of your daily supplement regimen.

### **Soak Up in Sun**

It's important to protect your skin from the direct sunlight. But our body needs some sun to make vitamin D. Always remember, getting light while driving cars and working in close offices with display windows will not help you, as they are closed by glass. So Try 15-20 minutes of sun a day, three times a week to maintain your Vit-D levels.

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## **References:**

1. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, D.C.: National Academies Press, 2010. <https://www.ncbi.nlm.nih.gov/books/NBK56070/>
2. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.
3. Norman AW, Henry HH. Vitamin D. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition, 10th ed. Washington DC: Wiley-Blackwell, 2012.

4. Jones G. Vitamin D. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. *Modern Nutrition in Health and Disease*, 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2014.
5. Silva MC, Furlanetto TW. Intestinal absorption of vitamin D: A systematic review. *Nutr Rev* 2018;76:60-76. [PubMed abstract]
6. Sempos CT, Heijboer AC, Bikle DD, Bollerslev J, Bouillon R, Brannon PM, et al. Vitamin D assays and the definition of hypovitaminosis D. Results from the First International Conference on Controversies in Vitamin D. *Br J Clin Pharmacol* 2018;84:2194-207. [PubMed abstract]
7. Holick MF. Vitamin D deficiency. *New England Journal of Medicine*. 2007 Jul 19;357(3):266-81.
8. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. *Archives of pediatrics & adolescent medicine*. 2004 Jun 1;158(6):531-7.
9. Lips PT. Worldwide status of vitamin D nutrition. *The Journal of steroid biochemistry and molecular biology*. 2010 Jul 1;121(1-2):297-300.
10. Robinson PD, Högler W, Craig ME, Verge CF, Walker JL, Piper AC, Woodhead HJ, Cowell CT, Ambler GR. The re-emerging burden of rickets: a decade of experience from Sydney. *Archives of Disease in Childhood*. 2006 Jul 1;91(7):564-8.
11. Kreiter SR, Schwartz RP, Kirkman Jr HN, Charlton PA, Calikoglu AS, Davenport ML. Nutritional rickets in African American breast-fed infants. *The Journal of pediatrics*. 2000 Aug 1;137(2):153-7.
12. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008 Aug 1;122(2):398-417.
13. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. *The Journal of Clinical Endocrinology & Metabolism*. 2007 Apr 1;92(4):1415-23.
14. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *Jama*. 2005 May 11;293(18):2257-64.
15. Cauley JA, LaCroix AZ, Wu L, Horwitz M, Danielson ME, Bauer DC, Lee JS, Jackson RD, Robbins JA, Wu C, Stanczyk FZ. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Annals of internal medicine*. 2008 Aug 19;149(4):242-50.
16. Cauley JA, Parimi N, Ensrud KE, Bauer DC, Cawthon PM, Cummings SR, Hoffman AR, Shikany JM, Barrett-Connor E, Orwoll E. Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. *Journal of Bone and Mineral Research*. 2010 Mar;25(3):545-53.
17. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Archives of internal medicine*. 2009 Mar 23;169(6):551-61.
18. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database of Systematic Reviews*. 2014(4).

19. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB. Effect of vitamin D on falls: a meta-analysis. *Jama*. 2004 Apr 28;291(16):1999-2006.
20. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *Journal of the American Geriatrics Society*. 2007 Feb;55(2):234-9.
21. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Archives of internal medicine*. 2006 Feb 27;166(4):424-30.
22. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009 Oct 1;339:b3692.
23. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. *Alimentary pharmacology & therapeutics*. 2009 Jul;30(2):113-25.
24. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case-control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *Journal of the National Cancer Institute*. 2007 Jul 18;99(14):1120-9.
25. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *American journal of preventive medicine*. 2007 Mar 1;32(3):210-6.
26. Giovannucci E. Epidemiological evidence for vitamin D and colorectal cancer. *Journal of Bone and Mineral Research*. 2007 Dec;22(S2):V81-5.
27. Lin J, Zhang SM, Cook NR, Manson JE, Lee IM, Buring JE. Intakes of calcium and vitamin D and risk of colorectal cancer in women. *American journal of epidemiology*. 2005 Apr 15;161(8):755-64.
28. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. *Nutrition and cancer*. 2008 Dec 31;61(1):47-69.
29. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, Hankinson SE. Plasma 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiology and Prevention Biomarkers*. 2005 Aug 1;14(8):1991-7.
30. Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, Newmark H, Holick MF, Garland FC. Vitamin D and prevention of breast cancer: pooled analysis. *The Journal of steroid biochemistry and molecular biology*. 2007 Mar 1;103(3-5):708-11.
31. Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM. Intakes of calcium and vitamin D and breast cancer risk in women. *Archives of Internal Medicine*. 2007 May 28;167(10):1050-9.
32. Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. *Cancer causes & control*. 2007 Sep 1;18(7):775-82.
33. Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, McCarty CA, Hollis BW, Graubard BI, Berg CD, Ziegler RG. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiology and Prevention Biomarkers*. 2008 Apr 1;17(4):889-94.



34. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *New England Journal of Medicine*. 2006 Feb 16;354(7):684-96.
35. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA. Calcium plus vitamin D supplementation and the risk of breast cancer. *JNCI: Journal of the National Cancer Institute*. 2008 Nov 19;100(22):1581-91.
36. Holick MF. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med*. 2006; 354:2287-8; author reply 2287-8.
37. Giovannucci E. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med*. 2006; 354:2287-8; author reply 2287-8.
38. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, Friedenberg G. Vitamin D supplements and prevention of cancer and cardiovascular disease. *New England Journal of Medicine*. 2019 Jan 3;380(1):33-44.
39. Keum N, Lee DH, Greenwood DC, Manson JE, Giovannucci E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Annals of Oncology*. 2019 May 1;30(5):733-43.
40. Giovannucci E. Expanding roles of vitamin D. *J Clin Endocrinol Metab*. 2009; 94:418-20.
41. Norman PE, Powell JT. Vitamin D and cardiovascular disease. *Circulation research*. 2014 Jan 17;114(2):379-93.
42. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *Jama*. 2010 May 12;303(18):1815-22.
43. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer?. *International journal of epidemiology*. 1980 Sep 1;9(3):227-31.
44. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: global perspective. *Annals of epidemiology*. 2009 Jul 1;19(7):468-83.
45. McCullough ML, Zoltick ES, Weinstein SJ, Fedirko V, Wang M, Cook NR, Eliassen AH, Zeleniuch-Jacquotte A, Agnoli C, Albanes D, Barnett MJ. Circulating vitamin D and colorectal cancer risk: an international pooling project of 17 cohorts. *JNCI: Journal of the National Cancer Institute*. 2019 Feb 1;111(2):158-69.
46. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, Kinkeldei J, Boehm BO, Weihrauch G, Maerz W. Independent association of low serum 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Archives of internal medicine*. 2008 Jun 23;168(12):1340-9.
47. Elamin MB, Abu Elnour NO, Elamin KB, Fatourehchi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *The Journal of Clinical Endocrinology & Metabolism*. 2011 Jul 1;96(7):1931-42.
48. Mitri J, Pittas AG. Vitamin D and diabetes. *Endocrinol Metab Clin North Am*. 2014 Mar;43(1):205-32.

49. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes care*. 2006 Mar 1;29(3):650-6.
50. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action. *Molecular aspects of medicine*. 2008 Dec 1;29(6):361-8.
51. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Archives of internal medicine*. 2008 Jun 9;168(11):1174-80.
52. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *The Journal of Clinical Endocrinology & Metabolism*. 2008 Oct 1;93(10):3927-35.
53. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, März W. Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke*. 2008 Sep 1;39(9):2611-3.
54. Booth TW, Lanier PJ. Vitamin D deficiency and risk of cardiovascular disease. *Circulation Res* 117. 2008;503:511.
55. Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, Aroda VR, Brodsky I, Ceglia L, Chadha C, Chatterjee R, Desouza C, Dolor R, Foreyt J, Fuss P, Ghazi A, Hsia DS, Johnson KC, Kashyap SR, Kim S, LeBlanc ES, Lewis MR, Liao E, Neff LM, Nelson J, O'Neil P, Park J, Peters A, Phillips LS, Pratley R, Raskin P, Rasouli N, Robbins D, Rosen C, Vickery EM, Staten M; D2d Research Group. Vitamin D Supplementation and Prevention of Type 2 Diabetes. *N Engl J Med*. 2019 Aug 8;381(6):520-530
56. Dobson R, Giovannoni G. Multiple sclerosis—a review. *European journal of neurology*. 2019 Jan;26(1):27-40.
57. Goldberg P. Multiple sclerosis: vitamin D and calcium as environmental determinants of prevalence: (A viewpoint) part 1: sunlight, dietary factors and epidemiology. *International Journal of Environmental Studies*. 1974 Jan 1;6(1):19-27.
58. Munger KL, Zhang SM, O'reilly E, Hernan MA, Olek MJ, Willett WC, Ascherio A. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004 Jan 13;62(1):60-5.
59. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *Jama*. 2006 Dec 20;296(23):2832-8.
60. Salzer J, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P. Vitamin D as a protective factor in multiple sclerosis. *Neurology*. 2012 Nov 20;79(21):2140-5.
61. Munger KL, Hongell K, Aivo J, Soilu-Hänninen M, Surcel HM, Ascherio A. 25-Hydroxyvitamin D deficiency and risk of MS among women in the Finnish Maternity Cohort. *Neurology*. 2017 Oct 10;89(15):1578-83.
62. Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, Freedman MS, Hartung HP, Miller DH, Montalbán X, Edan G. Vitamin D as an early predictor of multiple sclerosis activity and progression. *JAMA neurology*. 2014 Mar 1;71(3):306-14.
63. Fitzgerald KC, Munger KL, Köchert K, Arnason BG, Comi G, Cook S, Goodin DS, Filippi M, Hartung HP, Jeffery DR, O'Connor P. Association of vitamin D levels with multiple sclerosis activity and progression in patients receiving interferon beta-1b. *JAMA neurology*. 2015 Dec 1;72(12):1458-65.

64. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: from risk factors to prevention—an update. In *Seminars in neurology* 2016 Apr (Vol. 36, No. 02, pp. 103-114). Thieme Medical Publishers.
65. Gillespie KM. Type 1 diabetes: pathogenesis and prevention. *Cmaj*. 2006 Jul 18;175(2):165-70.
66. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *The Lancet*. 2001 Nov 3;358(9292):1500-3.
67. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *The Lancet*. 2016 Jun 4;387(10035):2340-8.
68. Munger KL, Levin LI, Massa J, Horst R, Orban T, Ascherio A. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. *American journal of epidemiology*. 2013 Mar 1;177(5):411-9.
69. Hope-Simpson RE. The role of season in the epidemiology of influenza. *Epidemiology & Infection*. 1981 Feb;86(1):35-47.
70. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. *Epidemiology & Infection*. 2006 Dec;134(6):1129-40.
71. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Archives of internal medicine*. 2009 Feb 23;169(4):384-90.
72. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *The American journal of clinical nutrition*. 2010 May 1;91(5):1255-60.
73. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017 Feb 15;356:i6583.
74. Zasloff M. Fighting infections with vitamin D. *Nature medicine*. 2006 Apr;12(4):388-90.
75. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *International journal of epidemiology*. 2008 Feb 1;37(1):113-9.
76. Chocano-Bedoya P, Ronnenberg AG. Vitamin D and tuberculosis. *Nutrition reviews*. 2009 May 1;67(5):289-93.
77. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Archives of internal medicine*. 2007 Sep 10;167(16):1730-7.
78. Giovannucci E. Can vitamin D reduce total mortality?. *Archives of Internal Medicine*. 2007 Sep 10;167(16):1709-10.
79. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hyppönen E, Berry J, Vieth R, Lanham-New S. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *The American journal of clinical nutrition*. 2012 Jun 1;95(6):1357-64.

80. Wilson LR, Tripkovic L, Hart KH, Lanham-New SA. Vitamin D deficiency as a public health issue: using vitamin D 2 or vitamin D 3 in future fortification strategies. *Proceedings of the Nutrition Society*. 2017 Aug;76(3):392-9.
81. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004; 79:362-71
82. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007; 357:266-81.

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